

PATENT
CASE IN0291K2GQ1B1C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of:
BISHOP ET AL. : Examiner: To Be Assigned
For Patent For: TRICYCLIC AMIDE AND : Group: To Be Assigned
UREA COMPOUNDS USEFUL FOR : Date: December 20, 2001
INHIBITION OF G-PROTEIN FUNCTION :
AND FOR TREATMENT OF :
PROLIFERATIVE DISEASES :
Serial No.: To Be Assigned : Prior Examiner:
: T. Truong
Filed: Herewith : Prior Group: 1624
Related To: This is a divisional of :
Application Serial No. 09/350,870 filed :
July 9, 1999 :
-----X

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

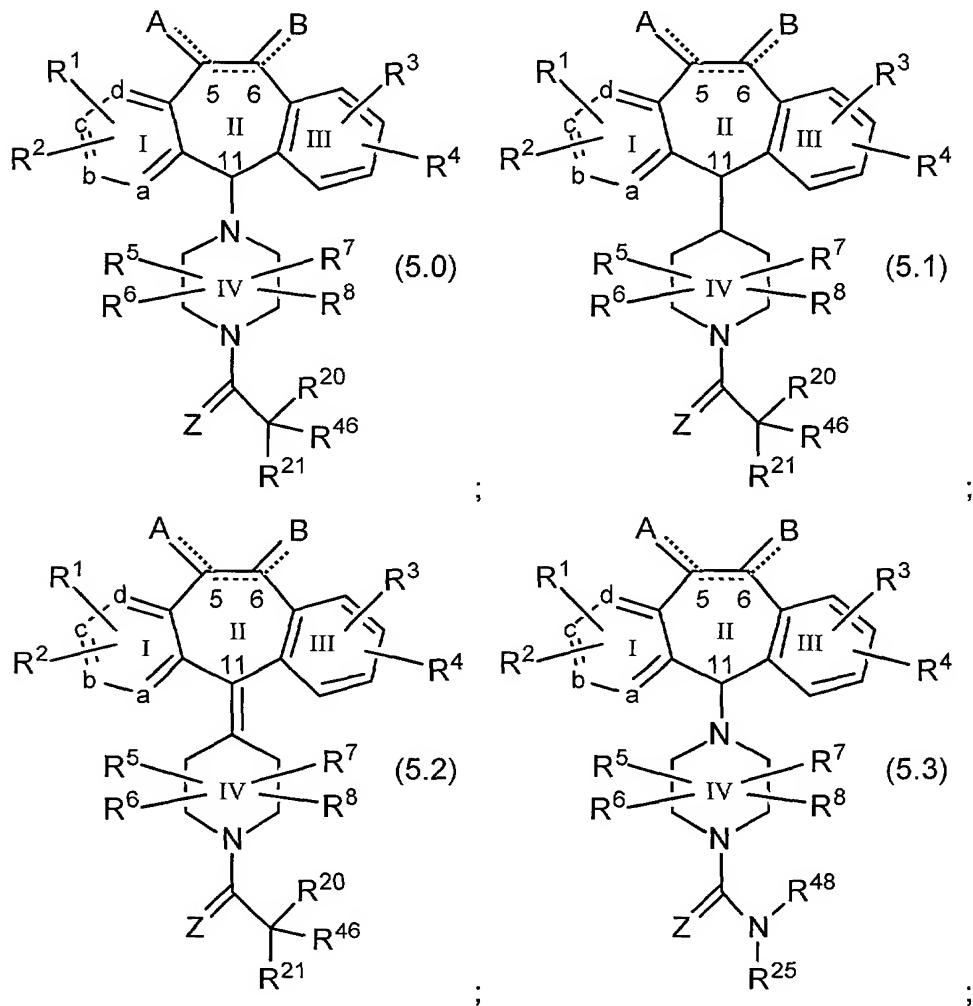
Please amend the above identified application as follows:

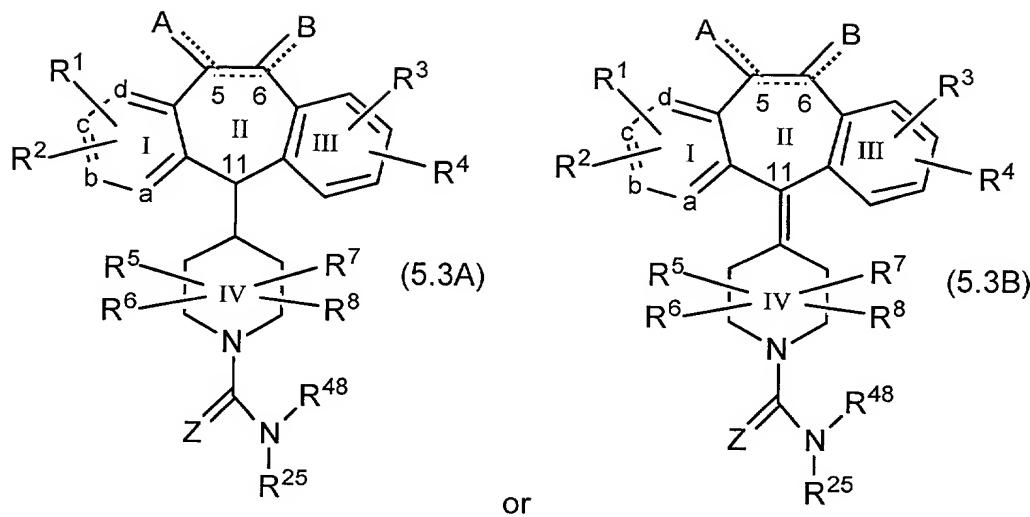
IN THE CLAIMS

Cancel Claims 1-12, and 22-27 without prejudice.

Replace Claim 13 with the like numbered claim below.

13. (AMENDED) A compound selected from a compound of the formula:

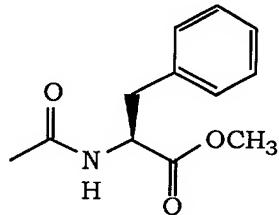




or a pharmaceutically acceptable salt or solvate thereof, wherein :

one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

each of a, b, c, and d are independently selected from CR¹ or CR²;
each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,



-SR¹¹N(R⁷⁵)₂ (wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring;

R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰,

-SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or one of R⁵, R⁶, R⁷ and R⁸ can be taken in combination with R⁴⁰ as defined below to represent -(CH₂)_r wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, -CF₃ or aryl, or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is combined with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, aryl, or aralkyl;

R¹¹ represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond, represented by the dotted line, to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂; H and halo, dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4;

R²⁰, R²¹ and R⁴⁶ are each independently selected from the group consisting of:

- (1) H;
- (2) -(CH₂)_qSC(O)CH₃ wherein q is 1 to 3;
- (3) -(CH₂)_qOSO₂CH₃ wherein q is 1 to 3;
- (4) -OH;
- (5) -CS(CH₂)_w(substituted phenyl) wherein w is 1 to 3 and the substituents on said substituted phenyl group are the same substituents as described below for said substituted phenyl;

- (6) -NH₂;
- (7) -NHCBZ;
- (8) -NHC(O)OR²² wherein R²² is an alkyl group having from 1 to 5 carbon atoms, or R²² represents phenyl substituted with 1 to 3 alkyl groups;
- (9) alkyl;
- (10) -(CH₂)_kphenyl wherein k is 1 to 6;
- (11) phenyl;
- (12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO₂, -OH, -OCH₃, -NH₂, -NHR²², -N(R²²)₂,

alkyl, $-\text{O}(\text{CH}_2)_t\text{phenyl}$ (wherein t is from 1 to 3), and $-\text{O}(\text{CH}_2)_t$ substituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

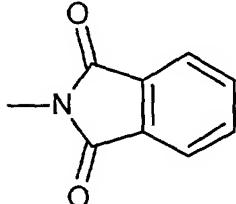
(16) cycloalkyl having from 5 to 7 carbon atoms;

(17) heteroaryl;

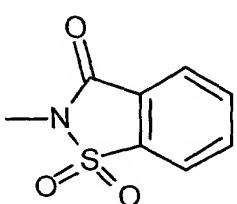
(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), $-\text{S}(\text{O})_t\text{R}^{11}$, or any of the substituents given above for said substituted phenyl, and said substituents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

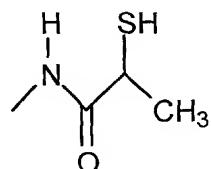
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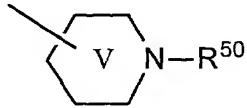


(22)



(23) $-\text{NHC(O)}-(\text{CH}_2)_k\text{phenyl}$ or $-\text{NH(O)}-(\text{CH}_2)_k$ -substituted phenyl, wherein said k is as defined above;

(24) piperidine Ring V:

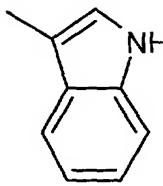


wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or $-\text{C}(\text{O})\text{NH(R}^{10})$ wherein R^{10} is H or alkyl;

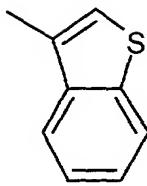
(25) $-\text{NHC(O)CH}_2\text{C}_6\text{H}_5$ or $-\text{NHC(O)CH}_2$ -substituted- C_6H_5 ;

(26) $-\text{NHC(O)OC}_6\text{H}_5$;

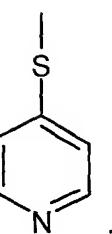
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(29)



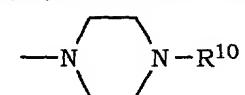
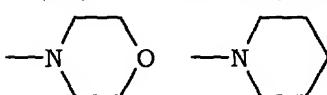
(30) -OC(O)-heteroaryl;

(31) -O-alkyl; and

(32) -CF₃;

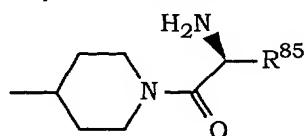
(33) -CN;

(34) a heterocycloalkyl group of the formula



; and

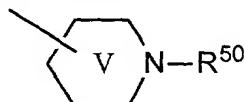
(35) a piperidinyl group of the formula



wherein R⁸⁵ is H, alkyl, or alkyl substituted by -OH or -SCH₃; or

R²⁰ and R²¹ taken together form a =O group and the remaining R⁴⁶ is as defined above; or

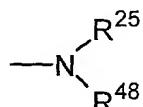
Two of R²⁰, R²¹ and R⁴⁶ taken together form piperidine Ring V



wherein R⁵⁰ is as defined above;

with the proviso that R⁴⁶, R²⁰ and R²¹ are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R⁴⁴ represents



wherein R²⁵ represents heteroaryl, N-methylpiperidinyl or aryl; and R⁴⁸ represents H or alkyl;

Z represents O or S; and
wherein for the compounds of Formula 5.2 the substituents R²⁰,
R²¹, and R⁴⁶ are selected such that when one of said substituents R²⁰,
R²¹, and R⁴⁶ is selected from the group consisting of: (1) H, (4) -OH,
(6) -NH₂, (8) -NHC(O)OR²², (9) alkyl, (11) phenyl, (17) heteroaryl,
(18) hydroxyalkyl, (19) substituted pyridyl, (12) substituted phenyl and
(31) -O-alkyl, then the remaining two of said substituents R²⁰, R²¹ and R⁴⁶
cannot both be H when: (a) R¹ and R² are both H, and (b) the double bond
between C-5 and C-6 is absent, and (c) both A and B are H₂, and (d) R⁴ is
H, and (e) R³ is H or Cl at C-8.

IN THE SPECIFICATION

On page 1, below the title, insert:

“REFERENCE TO RELATED APPLICATIONS

This is a divisional of Application Serial No. 09/350,870 filed July 9, 1999, which in turn is a continuation of Application Serial No. 08/971,038 filed November 14, 1997 (now abandoned), which in turn is a division of Application Serial No. 08/450,288 filed May 25, 1995 (now U.S. 5,696,121), which in turn is a continuation of Application Serial No. 08/410,187 filed March 24, 1995 (now U.S. 5,719,148), which in turn is a continuation-in-part of Application Serial No. 08/312,028 filed September 26, 1994 (now abandoned), which in turn is a continuation-in-part of Application Serial No. 08/137,862 filed October 15, 1993 (now abandoned)."

REMARKS

The amendments to Claim 13 incorporate the limitations of cancelled Claim 1.

Claims 13-21 remain in the Application.

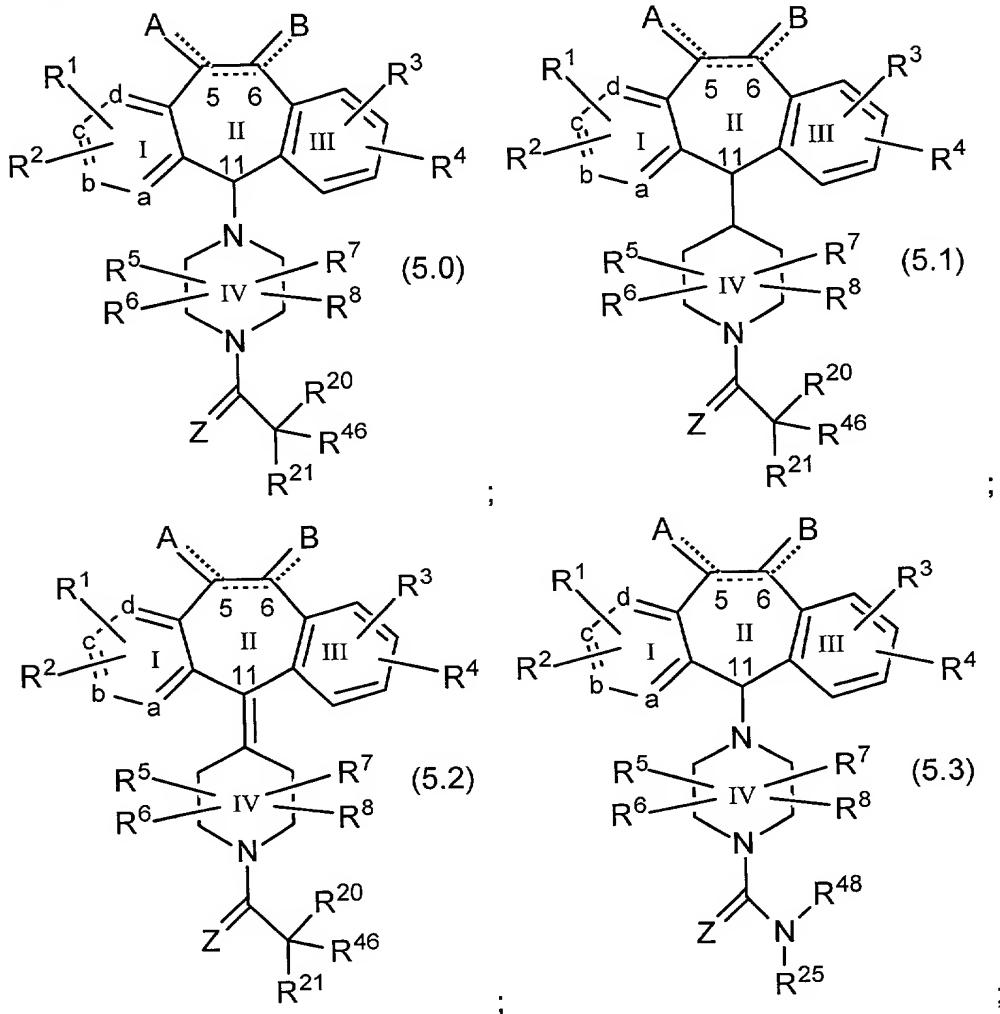
Respectfully submitted,

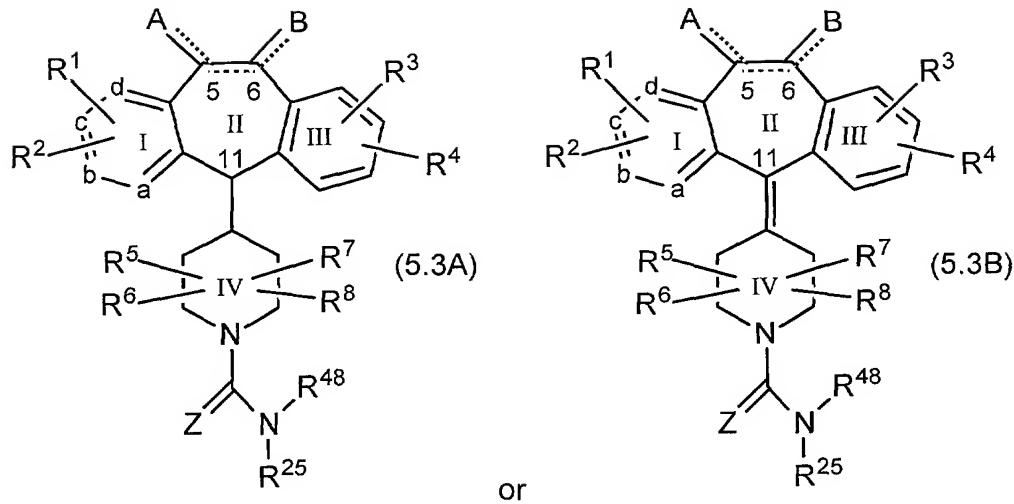

Henry C. Jeanette
Reg. No. 30, 856
Attorney for Applicants
(908) 298-5041

Doc. No. 21336v1

Claim Showing Amendments Made

13. (AMENDED) A compound selected from a compound of the formula:





or a pharmaceutically acceptable salt or solvate thereof, wherein :

one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

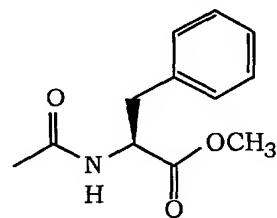
each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃,

-OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂,

-NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰,

-CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,



-SR¹¹N(R⁷⁵)₂ (wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰:

R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring;

R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰,

-SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰,
-OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or one of R⁵, R⁶, R⁷ and R⁸ can be taken
in combination with R⁴⁰ as defined below to represent -(CH₂)_r- wherein r is
1 to 4 which can be substituted with lower alkyl, lower alkoxy, -CF₃ or aryl,
or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is combined
with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, aryl, or aralkyl;

R¹¹ represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double
bond, represented by the dotted line, to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an
optional double bond, such that when a double bond is present, A and B
independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰, and
when no double bond is present between carbon atoms 5 and 6, A and B
each independently represent H₂, -(OR¹¹)₂; H and halo, dihalo, alkyl and
H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H, =NOR¹⁰ or
-O-(CH₂)_p-O- wherein p is 2, 3 or 4;

R²⁰, R²¹ and R⁴⁶ are each independently selected from the group
consisting of:

(1) H;

(2) -(CH₂)_qSC(O)CH₃ wherein q is 1 to 3;

(3) -(CH₂)_qOSO₂CH₃ wherein q is 1 to 3;

(4) -OH;

(5) -CS(CH₂)_w(substituted phenyl) wherein w is 1 to 3 and the
substituents on said substituted phenyl group are the same substituents
as described below for said substituted phenyl;

(6) -NH₂;

(7) -NHCbz;

(8) -NHC(O)OR²² wherein R²² is an alkyl group having from 1 to 5
carbon atoms, or R²² represents phenyl substituted with 1 to 3 alkyl
groups;

(9) alkyl;

(10) -(CH₂)_kphenyl wherein k is 1 to 6;

(11) phenyl;

(12) substituted phenyl wherein the substituents are selected from
the group consisting of: halo, NO₂, -OH, -OCH₃, -NH₂, -NHR²², -N(R²²)₂.

alkyl, -O(CH₂)_tphenyl (wherein t is from 1 to 3), and -O(CH₂)_tsubstituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

(16) cycloalkyl having from 5 to 7 carbon atoms;

(17) heteraryl;

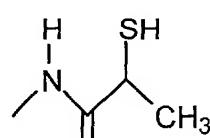
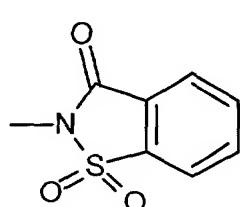
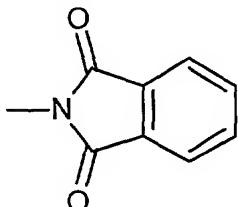
(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), -S(O)₂R¹¹, or any of the substituents given above for said substituted phenyl, and said substituents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

(20)

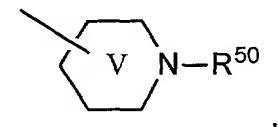
(21)

(22)



(23) -NHC(O)-(CH₂)_k-phenyl or -NH(O)-(CH₂)_k-substituted phenyl, wherein said k is as defined above;

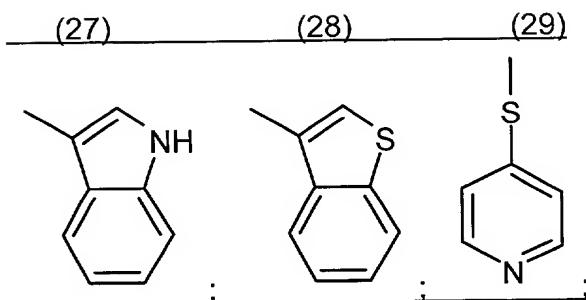
(24) piperidine Ring V:



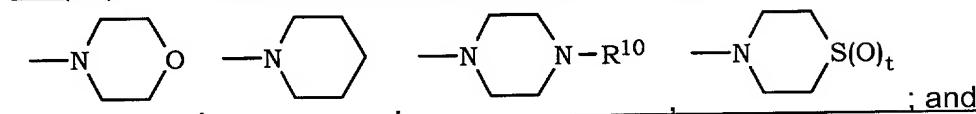
wherein R⁵⁰ represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or -C(O)NH(R¹⁰) wherein R¹⁰ is H or alkyl;

(25) -NHC(O)CH₂C₆H₅ or -NHC(O)CH₂-substituted-C₆H₅:

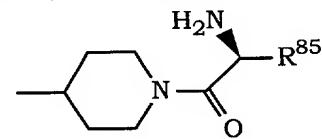
(26) -NHC(O)OC₆H₅:



- (30) -OC(O)-heteraryl;
- (31) -O-alkyl; and
- (32) -CF₃;
- (33) -CN;
- (34) a heterocycloalkyl group of the formula



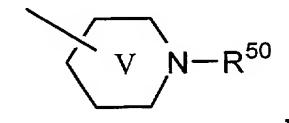
(35) a piperidinyl group of the formula



wherein R⁸⁵ is H, alkyl, or alkyl substituted by -OH or -SCH₃; or

R²⁰ and R²¹ taken together form a =O group and the remaining R⁴⁶ is as defined above; or

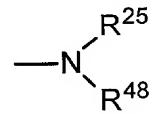
Two of R²⁰, R²¹ and R⁴⁶ taken together form piperidine Ring V



wherein R^{50} is as defined above;

with the proviso that R⁴⁶, R²⁰ and R²¹ are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R⁴⁴ represents



wherein R²⁵ represents heteroaryl, N-methylpiperdinyl or aryl; and R⁴⁸ represents H or alkyl;

Z represents O or S; and

【all the substituents are as defined in Claim 1, and】 wherein for the compounds of Formula 5.2 the substituents R²⁰, R²¹, and R⁴⁶ are selected such that when one of said substituents R²⁰, R²¹, and R⁴⁶ is selected from the group consisting of: (1) H, (4) -OH, (6) -NH₂, (8) -NHC(O)OR²², (9) alkyl, (11) phenyl, (17) heteroaryl, (18) hydroxyalkyl, (19) substituted pyridyl, (12) substituted phenyl and (31) -O-alkyl, then the remaining two of said substituents R²⁰, R²¹ and R⁴⁶ cannot both be H when: (a) R¹ and R² are both H, and (b) the double bond between C-5 and C-6 is absent, and (c) both A and B are H₂, and (d) R⁴ is H, and (e) R³ is H or Cl at C-8.